Chinese Color Nest Project (CCNP)[i]: Growing Up in China

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[i] This is the translational version of our paper describing the Chinese Color Nest Project, which has been published in *Chinese Science Bulletin*, 2017, 62: 3008-3022. All coauthors prepared the draft, which has been proof-read by a native English speaker from Child Mind Institute at New York: Dr. Jasmine Escalera.

Abstract: To face the challenges of keeping healthy in increasing population sizes of both ageing and developing people in China, a fundamental request from the public health is the development of lifespan normative trajectories of brain and behavior. This paper introduces the Chinese Color Nest Project (CCNP 2013–2022), a large-scale ten-year program of modeling brain and behavioral trajectories for human lifespan (6–85 years old). We plan to gradually collect the behavioral and brain imaging data at ages across the lifespan on nationwide and depict the normal trajectory of Chinese brain development across the lifespan, based on the accelerated longitudinal design in the coming next 10 years starting at 2013. Various psychiatric disorders have been demonstrated highly relevant to abnormal events during the neurodevelopment regarding their onset ages of first episodes. Therefore, delineation of normative growth curves of brain and cognition in typically developing children is extremely useful for monitoring, early detecting and intervention of various neurodevelopmental disorders. In this paper, we detailed the developing part of CCNP, devCCNP. It tracked 192 healthy children and adolescents (6–18 years old) in Beibei district of Chongqing for the first 5 years of the full CCNP cohort (2013–2017). To demonstrate the feasibility of implementing the long-term follow-up of CCNP, we here comprehensively document devCCNP in terms of its experimental design, sample strategies, data acquisition and storage as well as some preliminary results and data sharing roadmap for future. Specifically, we first describe the accelerated longitudinal sampling design as well as its exact ratio of sample dropping off during the data collection. Second, we present several initial findings such as canonical growth curves of cortical surface areas of a set of well-established large-scale functional networks of the human brain. Finally, together with records generated by many psychological and behavioral tests, we will provide an individual growing-up report for each family participating the program, initiating the potential guidance on the individual academic and social development. The resources introduced in the current work can provide first-hand data for a series of coming Chinese brain development studies, such as Chinese Standard MRI Brain Templates, Normative Growth Curves of Chinese Brain and Cognition as well as Mapping of Language Areas in Chinese Developing Brain. These would not only offer normative references of the atypical brain and cognition development for Chinese population but also serve as a strong force on accelerating the pace of integrating Chinese brain development into the national brain program or Chinese Brain Project.

Keywords: brain development, growth curve, Chinese color nest project, brain mapping, connectome

Introduction

Identifying the growth curve based on physiological or psychological measurements across the childhood and adolescence, as well as their typical characteristics of development at a certain age, can help to determine the critical period of development and whether a child reaches the normal level of development. Long-term pediatric practice on public health shows that growth curves are powerful tools for monitoring a process of growth. One example is the Child Growth Standards launched by the World Health Organization (WHO) in 2006 [1,2], which demonstrates that the median height of boys at the age of 5 years old is 110 cm, with three standard deviations above and below the median corresponding to the heights of 123.9 cm and 96.1 cm. Using this growth curve as reference, falling below the height of 96.1 cm as a 5-year old boy may suggest malnourishment or the presence of a developmental abnormality. Therefore, growth charts, a set of growth curves of physiological and psychological measurements, can help to indicate the necessity of early intervention and treatment for children with developmental diseases.

As early as the 1970s, the WHO released the international standards for the growth of children aged 5 to 19 years [3], and conducted a multi-center program regarding growth reference (from 1997 to 2003) for children under 6 years of age. Work completed by the program include a longitudinal study of infants from birth to 24 months and a cross-sectional survey of children from 18 months to 71 months [4]. In 2007, the existing growth curve was rebuilt by using a new statistical model [5]. The new reference for growth released by WHO includes height, weight, body mass index, head circumference, chest circumference and other anthropometric measurements. In addition to using it to assess nutritional status of children, many countries also include it as one of the indices of national wellbeing and require that public health policies make reference to it.

Promoted by the national population census that was supported by the Ministry of Health, domestic public health and pediatric institutions have built complete growth curves of height, weight, head circumference and trace elements in Chinese children and adolescents. These works were based on the modeling methodologies of WHO and US National Center for Disease Control (CDC) and greatly contributed to the clinical monitoring of growth of Chinese children and adolescents. The Department of Growth and Development, Capital Institute of Pediatrics, and Institute of Child and Adolescent Health of Peking University, jointly developed standardized growth curves of height and weight for children 0 to 18 years old [6]. Among these, the data for children 0 - 6 years old comes from the large-scale census project of “The National Growth Survey of Children under 7 Years in Nine Cities of China” organized by the Ministry of Health. In addition, the data for children and adolescents 7 - 19 years old comes from the “2005 Chinese Student Physique and Health Survey” organized by the Ministry of Education and the included nine cities (Beijing, Harbin, Xi'an, Shanghai, Nanjing, Wuhan, Guangzhou, Fuzhou and Kunming). Samples under the age of 7 years were divided into 22 age groups. Random cluster sampling was conducted according to age group distance. A total of 69,760 healthy children were investigated, including 34,901 males and 34,859 females. Healthy children and adolescents aged 6-19 years were selected by cluster sampling within the nine cities and their surrounding areas. The schools to be sampled were determined and stratified by age, with

the classroom as a unit for random cluster sampling. Finally, a total of 24,542 children and adolescents were selected, including 12,188 males and 12,354 females [7]. In 2010, Li and colleagues employed the aforementioned dataset to construct growth curves of weight, length and head circumference for newborns from birth to 6 months with one-month intervals [8]. In addition to these anthropometric measurements, Jin and colleagues also revised the "Chinese Development Scale for Children" that assesses the neuropsychological development of children in the Beijing area. They re-constructed the test items into five facets, including gross motor function, fine hand movement, adaptive ability, language, and social behavior, based on child cognitive development theory [9]. They also selected 2402 children, including 1265 males and 1137 females ages 0 - 60 months to revise the norms and reliability analysis in the Beijing area [10,11].

The clinical epidemiological surveys show that brain dysfunction has brought enormous social and economic burdens to various countries, and can occur at any stage across the human lifespan [12,13]: 50% of those with mental disorders were diagnosed before the age of 14, and up to 75% of patients, if the age of onset is extended to 24 [14,15]. Studies have shown that such disorders can be identified in certain critical time windows. For example, destructive and impulsive behaviors and anxiety are prone to occur in childhood, whereas mood disorders, psychiatric disorders, and drug abuse are more likely to have their onset during puberty [16-20]. The National Institute of Mental Health's (NIMH) Strategic Plan emphasizes that in the field of brain and behavioral sciences, special attention should be paid to the scientific researches of lifelong development of brain functions and mental disorders. Determining the statistical norm of specified brain circuits will enable researchers to understand the pathophysiology of the entire developmental process of psychiatric disorders (http://www.nimh.nih.gov/about/strategic-planning-reports/strategic-objective-2.shtml). Human brain magnetic resonance imaging (MRI) technology has been widely used in the field of fundamental researches of brain development [21] and gradually being used in studies of brain developmental trajectories in children and adolescents [22-25]. It is expected to be a supportive tool for early detection, objective diagnosis, and course monitoring of various brain functional diseases [26-29]. However, studies implementing growth curves of brain cognition and child and adolescent behavior are still rare, which may be indicative that growth curve studies have not yet received enough attention from fundamental brain sciences. Recently, with the development and advancement of the brain plans in many countries and areas [30,31], the relationship between human brains and psychological behaviors has received more and more attention and is becoming one of the core contents in brain science research. For example, "Human Connectome Project (HCP: 2009-2015)" launched in the United States that focuses on the macro-scale human brain connectome and psychological behaviors has achieved a series of advancements [32,33]. Similarly, the National Institute of Health (NIH) in the United States has completed the deployment of three projects including the Infant Connectome, the Adolescent Brain and Cognitive Development, and the Human Brain Lifespan Development, based on the latest development in HCP [34].

Focusing on the international frontier of brain sciences with the support of the National Natural Science Foundation, Chinese Academy of Sciences (CAS), Ministry of Science and Technology, and Beijing Municipal Science & Technology Commission, Chinese

scientists have initiated studies of growth curves of the human brain earlier (2012) than the US HCP, and have put forward the "Chinese Color Nest Project (CCNP: 2013-2022)", which will nationwidely collect behavioral and brain imaging data at all ages across the human lifespan [35,36]. CCNP will determine the normal trajectory of Chinese brain development in the next 10 years. As the developing part of CCNP, devCCNP has been tracking 192 healthy children and adolescents (6-18 years old) in Beibei District of Chongqing for 5 years, demonstrating that the program is a feasible long-term initiative [37,38]. This paper will give a detailed introduction of devCCNP to its experimental design, sample collection strategy, data acquisition and storage, preliminary results, data sharing, existing problems and challenges, future research plans, and arrangements.

Experimental Design and Sample

Modeling a brain development curve requires the age distribution of the sample be of sufficient span and longitudinal tracking with certain time intervals. Studying the individual differences of brain structure also requires a certain number of subjects of the same age in order for statistical results to be generalizable. As a lifespan development research program, CCNP adopted longitudinal and cross-sectional mixed designs because a purely longitudinal design is difficult to implement in human subjects and a purely cross-sectional design cannot accurately characterize changes within the individual [39-41]. The devCCNP is committed to modeling the growth curve of brain cognition in children and adolescents. Until devCCNP was put forward, the brain-imaging field was lacking in longitudinal datasets which model brain structure and a functional growth curve. A few large-scale brain development datasets contain only cross-sectional structural magnetic resonance imaging (sMRI), diffusion tensor magnetic resonance imaging (dMRI) and resting functional magnetic resonance imaging (rfMRI) data [42,43]. The specificity of these datasets greatly limits the statistical strength and sensitivity of growth curves modeling. In order to model the brain growth curve accurately, we use a multi-cohort structured longitudinal design [40] to establish a standardized large-scale longitudinal dataset that covers multimodal brain imaging, cognitive, and behavioral measurements. The advantages of this design include the following: 1) the multi-cohort longitudinal design can systematically track the changes of brain and behavior of subjects, and can effectively control the influence of external environment factors such as season and climate on the physiological and psychological development of subjects. It also can ensure that multiple measurements of longitudinal tracing cover all ages; 2) the structured design within the cohort ensures that each measurement can cover all age stages and that sufficient cross-sectional data is collected to study the age characteristics and individual differences; 3) the mixed design can not only track the brain and behavioral changes of individuals in a systematic way, but also can expand the cross-sectional samples so that the fitted normal trajectory of development is more representative of the population; 4) the multi-cohort structured design avoids the defects of longitudinal tracking to some extent (such as time-consuming, high rate of dropping off).

Sampling Strategy

The age range of participants at baseline recruitment was 6.0-17.9 years, divided into 12 age groups separated by 1 year increments. The longitudinal interval was 15-months for each cohort (to avoid seasonal effects). Each age group contained 16 participants (8 males and 8 females). For each subject, the tracking period was 30 months, including three measurement time points (baseline, track 1 [15th month after the baseline], track 2 [30th month after the baseline]). Therefore, each subject received three MRI scans and cognitive-behavior measures. Figure 1 depicts details of the sampling strategy.

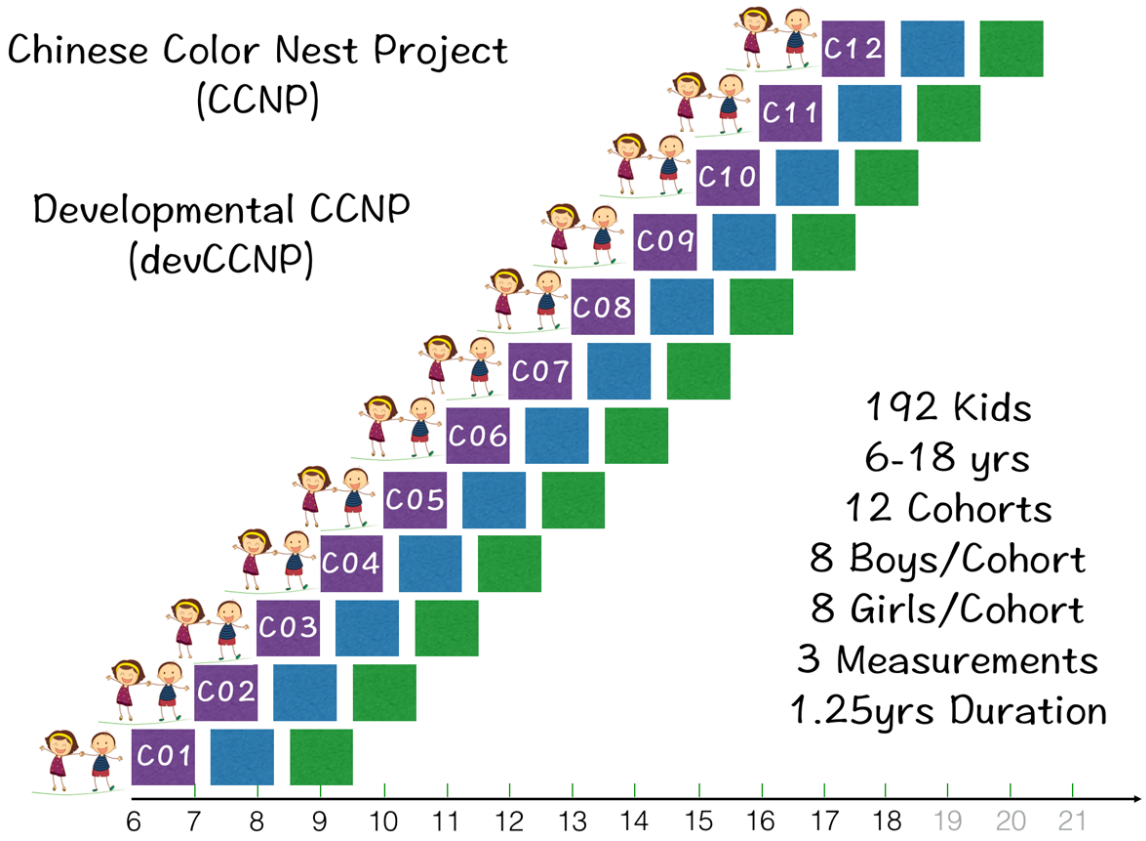

Figure 1 Sampling Strategy. Three waves were included: baseline (purple), follow-up 1 (blue), follow-up 2 (green), with a 15-month interval each, ranging from 6 to 18 years old (12 cohorts) on baseline.

Recruitment Strategy

The target sample as a whole will be community ascertained and we consider fully optimizing the representativeness of the sample to encompass variations across geographic, ethnic, racial and socio-economic groups. The pilot project chose the communities in the Beibei district, Chongqing, and was jointly conducted by the Institute of Psychology, CAS and the Faculty of Psychology at Southwest University. A primary school, a middle school, and a high school were included in the project, providing access to children enrolled from the first grade of primary school to the second grade of high school. The project is dedicated to the overall growth and development monitoring of these school-age children, providing

a five-year physical and mental development report for each child. We held project promotion sessions with the parents and schools and led activities of in to promote educating families about the recent advances in brain development science. The project team evenly distributed the data collecting works of all subjects throughout the five years in order to avoid collecting samples in concentrated timeframes which would interfere with the experimental results.

Exclusions: 1) Demographic: subjects are excluded due to inadequately detailed family histories; 2) Pregnancy, birth and perinatal history: known intra-uterine exposures capable of altering brain structure or function (teratogenic medications, any illicit drug use, smoking >1/2 pack per day or > 2 alcoholic drinks per week during pregnancy), hyperbilirubinemia requiring transfusion and/or phototherapy (>2 days), multiple birth, infant resuscitation by chest compression or intubation, birth weight<1500gm or >4200gm; 3) Physical/medical or growth: current height or weight < the 3rd percentile, or head circumference < the 3rd percentile by National Center for Health Statistics 2000 data, history of significant medical or neurological disorder with CNS implications (e.g., seizure disorder, CNS infection, malignancy, diabetes, systemic rheumatologic illness, muscular dystrophy, migraine or cluster headaches, sickle cell anemia, etc.), significant closed head injury (e.g., loss of consciousness), malignancy, hearing impairment requiring intervention, visual impairment requiring more than conventional glasses (e.g., strabismus, visual handicap), metal implants or current positive pregnancy test; 4) Behavioral/psychiatric: current or past treatment for language disorders (simple articulation disorders not exclusionary), lifetime history of Axis I psychiatric disorder ascertained by semi-structured interview (i.e., Schedule for Affective Disorders and Schizophrenia for Children-PL) (except for simple phobia, adjustment disorder, enuresis, encopresis, nicotine dependency), any Child Behavior Checklist (CBCL) subscale score ≥ 70, Wechsler Intelligence Scale for Children-IV-Chinese Version WISC-IV < 80; 5) Family history: history of inherited neurological disorder, history of mental retardation due to non-traumatic events in any first-degree relative, any first-degree relatives with lifetime history of schizophrenia, bipolar affective disorder, psychotic disorder, alcohol or other drug dependence, obsessive compulsive disorder, Tourette's disorder, major depression, ADHD or pervasive developmental disorder.

Phenotypic Assessment and Data Collection

The project assesses routine behavioral and neuropsychological measurements. The team's international partners have demonstrated the feasibility of large-scale phenotypic data measurements in a lifespan development study based on brain imaging [39]. We have used Chinese versions of these measurements in the current project. For each subject, the assessment process is as follows: 1) the guardians of children signed informed consent and filled out the basic information questionnaire and CBCL; 2) height, weight, pulse and blood pressure measurements were obtained; 3) magnetic resonance imaging scans were conducted; 4) Wechsler intelligence tests, behavioral assessments, and psychological tasks were performed. In order to prevent the physical fatigue and emotional fluctuations of children caused by behavioral tests to influence the brain scanning, all psychological behavior scales and tasks were completed after MRI scanning, on the same day or a few

days later. Table 1 and Table 2, respectively, list the detailed information of psychological behavioral scales and psychological experimental tasks. The following is a detailed introduction to the Wechsler Intelligence test and MRI scan-related phenotypic assessment.

Insert <Table 1 Psychological Behavioral Scales> about Here

Insert <Table 2 Psychological Experimental Tasks> about Here

Wechsler Intelligence Scale: We adopted the fourth edition of Wechsler's Child Intelligence test (Wechsler Intelligence scale for Children-IV-Chinese Version, WISC-IV) [71,72]. The test is applicable to children aged 6-16 years, including 10 core subtests and 4 supplemental subtests. Through synthetic scores, we can get a Full-Scale IQ (FSIQ) and 4 indices (verbal comprehension index, perceptual reasoning index, working memory index, and processing speed index). The ten core subtests include block design, similarities, digit span, picture concepts, coding, vocabulary, letter-number sequencing, matrix reasoning, comprehension, and symbol search. Supplemental subtests include information, picture completion, arithmetic, and cancellation. As an alternative to the core subtests, supplemental subtests can provide a broader sample of cognitive and intellectual functions. These scores span the four indices: similarities, vocabulary, comprehension, and information constitute the index of verbal comprehension; block design, picture concepts, matrix reasoning and picture completion constitute perceptual reasoning index; digit span, letter-number sequencing, and arithmetic form the working memory index; coding, symbol search, and cancellation constitute the processing speed index. Four indices reflect the cognitive ability of children in different cognitive fields, and the FSIQ reflects the overall cognitive ability of children. The original scores of each subtest can be normalized as scale scores, including the verbal comprehension, perception reasoning, working memory, processing speed and the total score of each scale. Finally, one retrieves the synthetic scores, the four indices and FSIQ. Scaled scores and synthetic scores are normally distributed, with the mean of the scale scores as 10 with a standard deviation of ±3 and the mean of the standard scores as 100 with a standard deviation of ±15.

The test was performed one-to-one by subject with an examiner who had been certified. The WISC-IV has high reliability and validity. The split-half reliability of each subtest is greater than 0.71, and is between 0.87~0.97 for synthetic scores. The test-rest reliability of each subtest at one month interval is between 0.71~0.86, and is greater than 0.80 for synthetic scores. The rater’s consistency reliability is between 0.96~0.99. WISC-IV has good convergent validity and discriminant validity, and the correlation between the functional approximation tests is higher than that of the different functions. The exploratory factor analysis showed that the fitness of four factors was in good agreement with the original structure, and the correlation coefficient with WISC-R's synthetic score and total scale score was between 0.6 ~ 0.74. Studies on supernormal children and children with mental disorders and learning disabilities further proved the validity of the Chinese Version of WISC-IV [71-73].

MRI Scans: MRI scanning was performed at the brain-imaging center in Southwest University with 3.0T Siemens Tim Trio MRI scanner, equipped with a Siemens 12-channel phased-array head coil and a 32-channel phased array coil. The scans consisted of two repeated resting-state scans, a T1-weighted imaging and a T2-weighted imaging. The scanning order is "positioning image scan--resting-state scan--T1-weighted anatomical image scan--resting-state scan--T2-weighted anatomical image scan". Here T2-weighted images are only used for auxiliary diagnoses to exclude brain lesions. During the execution of the project, the machine did not undergo any hardware or software upgrades.

A high-resolution T1-weighted anatomical image is acquired using a 3D Magnetization Prepared Rapid Gradient Echo (MP-RAGE), with the following parameters: Flip Angle (FA)=8°, time to inversion (TI)=900ms, time echo (TE)=3.02ms, time repetition (TR)=2600ms, Bandwidth per Voxel=180Hz, Partial Fourier=6/8, Number of Slices=176, slice phase encoding direction is from anterior to posterior, slice acquisition order is sequential ascending, Slice Thickness = 1ms, Slice Gap = 0.5ms, field of view (FOV) = 256mm, Acquisition Matrix = 256×256, Slice In-Plane Resolution = 1.0×1.0mm², Scan Duration = 8 minutes and 19 seconds.

The resting-state scan sequence is the Echo Planar Imaging (EPI), and the scan parameters are as follows: FA = 8°, TE = 30ms, TR = 2500ms, Bandwidth per Voxel = 2240Hz, Number of Slices = 38, Slice Orientation is the Axial, Slice phase encoding direction is from anterior to posterior, Slice acquisition order is interleaved ascending, Slice Thickness = 3mm, Slice Gap = 0.33mm, FOV = 216mm, Acquisition Matrix = 72×72, Slice In-Plane Resolution = 3.0×3.0 mm², Number of Measurements = 184, Scan duration = 7 minutes and 45 seconds, Fat Suppression is open during scanning.

Project Progress and Growth Reports

After one-year preparation, we launched CCNP in Beibei District, Chongqing. We held nine rounds of project promotion for students, parents and teachers in local primary, middle, and high schools. A total of 198 students and their parents volunteered for the first wave (base line) of data collection, providing informed consent signed by both themselves and their guardians. Among all subjects, the following were excluded: 2 subjects for an FSIQ below 80; 1 subject for usage of antidepressant medication; 1 subject for claustrophobia; 2 subjects for a brain cyst. The first wave started in December 2013 and ended in July 2014. The second wave (the first follow-up) was conducted from April to August in 2015, with a total of 158 subjects participating. Among them, 152 subjects had participated the first wave. The drop-off rate was 20.83%. In addition, 7 subjects were new joined volunteers with 1 child being excluded for behavioral problems. The third wave (the second follow-up) was carried out from September 2016 to January 2017. A total of 107 children participated, including 100 subjects for the third time, 5 subjects for the second time and 2 subjects for the first time. The drop-off rate was 33.54%. Details of subjects' age distribution are listed on Table 3. The information of phenotypic data collection is listed on Table 4.

Insert <Table 3 Age Distribution of Sample Size> about Here

Insert <Table 4 Completion of Phenotypic Assessments> about Here

After each wave of data collection, the project team generated reports of individual growth for every participant including those who were initially excluded. The report which provided information about the participant's physical, psychological, behavioral and cerebral development, was sent to guardians. So far, we have provided 198 reports for the first wave and 164 for the second wave. Reports for the third wave will be completed and provided to participants' families before December 2017.

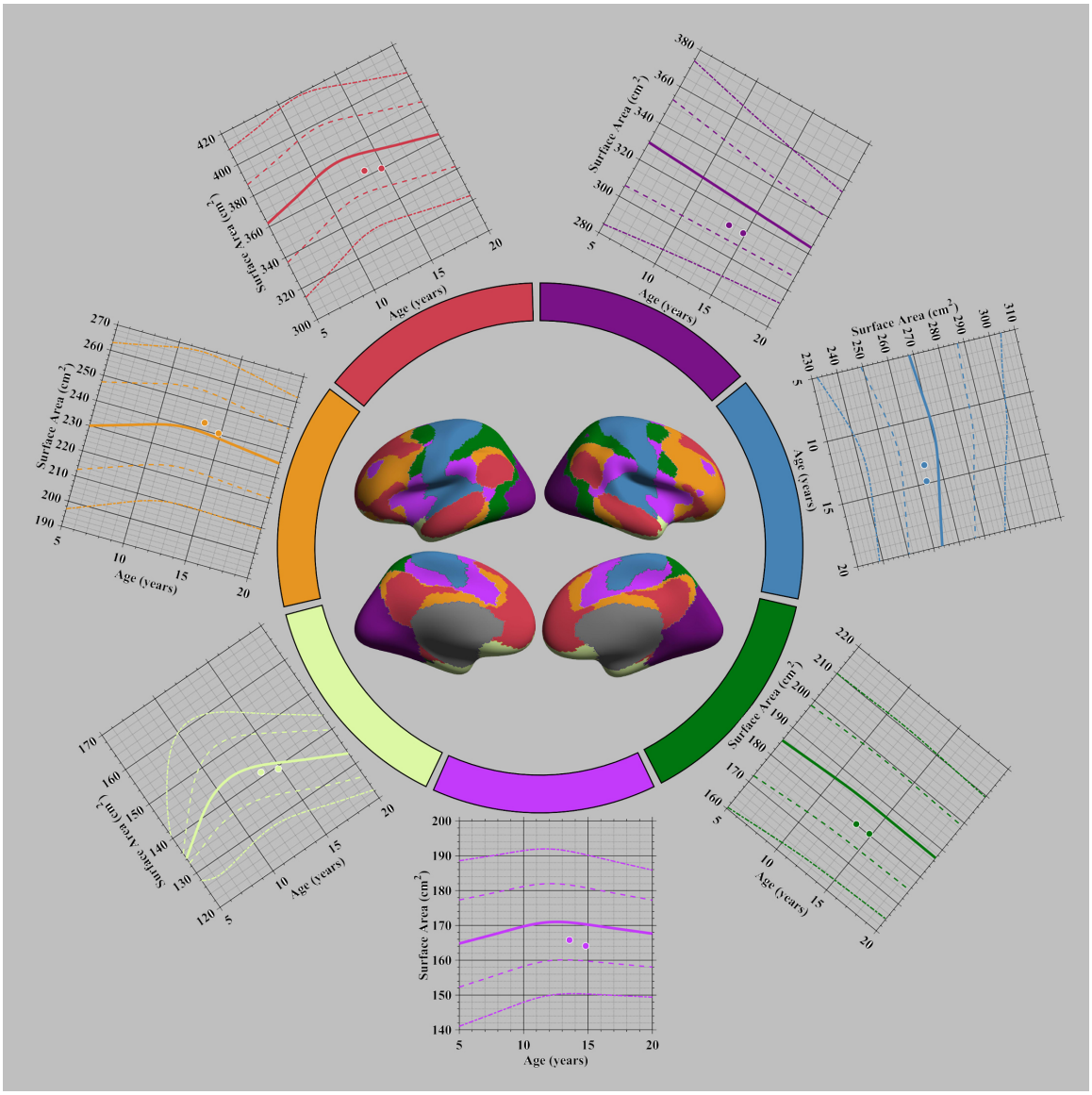

Figure 2 Growth curve of brain network surface area and individual application.

The growth report is a periodic presentation of the participants' physical and mind development. The report is based on the real data and objectively fed back to subjects' families. Appropriate and effective communication on our part has helped children and

their guardians understand the reports. The growth report included five measurement domains, including physical indices (height, weight, head circumference, blood pressure, pulse), intelligence quotation, emotional indices (social anxiety, depression, stress, behavioral problem), personality, and brain indices. The measurements of brain development are made up of total brain volume, subcortical gray matter volume, gray matter volume, white matter volume and cerebrospinal fluid volume, as well as cortical thickness and surface area of the seven brain networks [74], which consist of visual, somatomotor, dorsal attention, ventral attention, frontoparietal, limbic, and default networks. Referring to the modeling methods of the WHO's height and weight growth curves [2], we plotted group-level growth curves of each measurement. The individual data were plotted in each report. Figure 2 shows the development of cortical area of brain functional networks. A sample of the growth report in the supplementary material shows specific growth of each subject. This report was generated from data collected during the second wave. The second wave's reports contain all the content from the first wave's reports as well as comparisons between the two waves, along with suggestions for the subjects' families. In addition, we added the second wave's scores of the Children's Depression Inventory and Children Loneliness Scale, as well as second wave's contrast, enabling parents to better understand psychological healthy of their children.

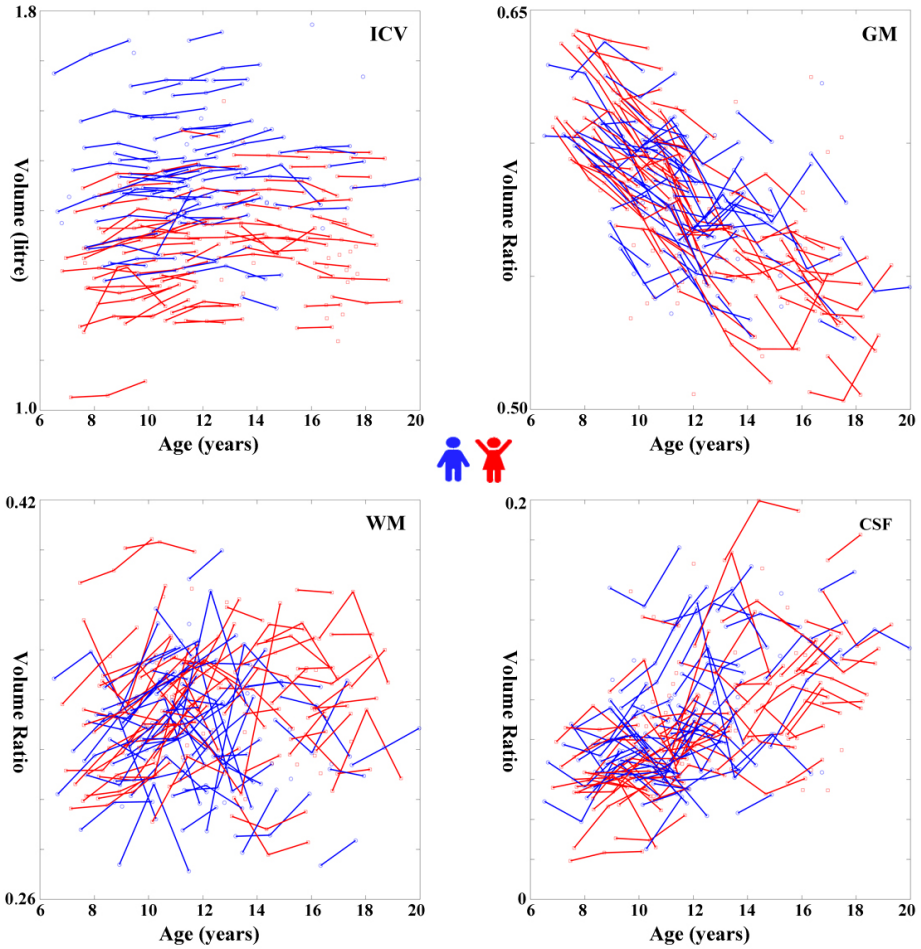

Figure 3 Absolute brain volume and tissues' relative volumes illustrated as Spaghetti plots

After strict quality control, we collected 393 qualified brain images from 179 subjects. A total of 80 subjects (44 females) completed all waves of the scan, 54 subjects (28 females) completed the first two waves of the scan, and 45 subjects (32 females) only completed the base line scan. We applied *volBrain* [75], an online automatic MRI brain volumetry system, to obtain the intracranial volume, the gray matter volume, the white matter volume and the cerebrospinal fluid volume. Due to individual variance of brain volume, we normalized the grey matter volume, the white matter volume and the cerebrospinal fluid volume by dividing the intracranial volume, calculating the proportions of these three tissues' volume to the intracranial volume. Figure 3 shows individuals' longitudinal scatter plots of absolute brain volume, relative grey matter volume, white matter volume and cerebrospinal fluid volume respectively.

Discussion

The present paper systematically introduced CCNP and demonstrated the feasibility of the project as a long-term study. CCNP is a longitudinal study focused on measuring the psychological behavior and neuro-cognitive characteristics of school-age children. At present, specific guidelines for launching the psychological health construction have been developed in China. It is crucial to make China a more competitive nation in regard to ensuring that every child grows up healthily and happily. The developed countries have deemed it a major focus in fundamental clinical and public health research to study mental health disorders as developmental phenomena [76,77]. In China, research on children's mental health is developing. Clinical diagnoses and preventions for severe cases of mental health, like autism and schizophrenia [78-80], are relatively weak and need more support.

A non-negligible problem in MRI research about normal brain development is the deviation in brain registration. Due to the lack of MRI data of children, early studies generally adopted adult brain template, like MNI152 [81] or the Talairach template [82], while registering children's MRI images. However, plenty of studies have pointed out that since there are large differences between children and adults brain shapes, adopting adult templates could cause non-negligible systematic deviations [83-85], affecting measurements of brain structures like grey and white matter proportions [86], cortical thickness [87], etc. To solve this problem, investigators have started to develop brain templates for different age cohorts of children. In America, Sanchez et al. [88,89] constructed age-specific MRI templates for western children from 2 weeks to 4 years old, and 4.5 to 19.9 years old respectively, with a 0.5-year interval, using data from both 1.5T and 3.0T MRI scanners. However, there also exists systematic deviations when registering Chinese MRI data to western templates, due to potentially possible differences between the races and their environments [90]. To solve this problem, the Medical College of Shandong University and Xuanwu Hospital affiliated with the Capital Medical University have constructed brain templates for Chinese adults [91-93]. In addition, Hong Kong University and the West China Hospital affiliated with the Sichuan University have constructed templates for Chinese children [94,95]. These templates for children were based on small samples and lack tests and researches with longitudinal MRI data. The former dataset was based on a single template of 53 children's data, ranging from 5 to 8 years old, ignoring the differences in brain structures among age cohorts. The latter templates contained five

templates for five age cohorts at an interval of 2 years. Each age cohort contained 20 to 39 subjects. Because the ages of these subjects are discrete, the templates cannot depict the development curve of the brains. Thus, under the current circumstances, constructing templates for children from different age cohorts is highly valuable for fundamental and clinical research in China and can have direct effects on measuring pediatric brain structure and function, as well as on the precision and reliability of constructing a Chinese brain development norm. CCNP has provided fundamental data to solve this scientific problem.

It is urgent to promote sharing Chinese children MRI data. Growth curves or development norms generally need support of large samples and big data. As a testament to this need, height and weight development norms constructed by WHO adopted a sample which contained 8440 children from 6 sites [1,2]. In China, the National Health and Family Planning Commission conducted a research project to measure physical development of children under 7 years old in 9 cities in 2005 which included 69760 children. The Ministry of Education launched a research project to measure 24542 Chinese students' physique and health in 2005 [6,7]. Since it is more complex and of higher cost than physiological measurement, MRI studies usually have much smaller sample sizes. Benefiting from international major data sharing projects, researchers could use a large amount of free MRI data publicly shared by different institutes around the world, which has solved the sample-size problem to a certain extent. Some famous data sharing projects are the 1000 Functional Connectomes Project (FCP) [96,97] and Human Connectome Project (HCP) [98,99] in the USA and the Consortium for Reliability and Reproducibility (CoRR), the first big data sharing project of brain imaging in China [38]. The brain template for western children constructed by Sanchez [88,89] benefitted from public neuroimaging data as well. The data they used was from 6 sites, although most of the MRI data was collected from the Pediatric MRI Data Repository (HIHPD) funded by NIH and data collected in the McCausland Brain Image Center at the University of South Carolina. In contrast, children's MRI data sharing projects are improving rather slowly. Only the CoRR [38] and ADHD2000 [100] initiatives contain children's MRI data. This is holding back the construction of developmental norms for children. Small sample sizes and samples that do not represent the population will result in regional representations. Lacking longitudinal data will make it impossible to construct a longitudinal development curve. In the future, by relying on national research projects, once different research teams in different regions publicly share the children MRI data, those problems would be solved. These initiatives will greatly promote research regarding the brain imaging of children and deepen our understanding of developmental patterns of Chinese children and adolescents' brain and related pathological mechanisms.

Due to the special nature of working with children and adolescents, studies involving these populations usually encounter additional difficulties, like ensuring and effectively communicating the safety, recruitment, organization, and implementation of the study. It is equally important to consider that the study not cause a delay in the children's academic development, which requires cooperation from schools. According to the developing situation in China, only projects including children and adolescents that are carried out by national ministries (such as the Ministry of health, Ministry of Education), can cover a wide range of subjects and meet adequate safety and organization requirements. For example, the Chinese children physiological (height and weight)

development project was promoted by the National Health and Family Planning Commission and the Ministry of education's effective and efficient organization. More attention and support from Chinese national ministries and commissions needs to be placed on imaging studies which focus on constructing Chinese brain development curve. Once the challenges of carrying out large-scale research is solved, these studies have the ability to promote progress in learning about Chinese brain development and more far-reaching general Chinese brain sciences. CCNP has verified the feasibility to collect data across various regions in order to compose a human brain development curve. By considering the famous Decade of Brain in the United States during the end of last century, we can see our biggest achievement would be to depict the curves of brain morphological development. At present, brain projects are vigorously promoted around the world. China should seize the opportunity other nations have already taken and utilize the advantage of having the world's largest population to carry out research programs focused on brain and cognitive growth norms that will enhance China's ability to influence related research fields throughout the world, while considering the effects these programs may have on China's aging society and fertility policies.

Acknowledgements

This research project was supported by the International Cooperation of the National Natural Science Fund (81220108014), key projects of the Chinese Academy of Sciences (CAS: KSZD-EW-TZ-002), Study on life cycle development trajectory of human brain functional connectome (81171409), human visual perception data computation and organization (2015CB351702).

The smooth running of the project was benefitted from the strong support from people and places such as the Faculty of Psychology, Southwestern University and Institute of Psychology, Chinese Academy of Sciences, and from the assistance and propaganda permission provided by the participated primary and middle schools in Beibei District, Chongqing. Thanks Liu Xun, Cao Xiaoyan, and Li Su for advices on project design. Thanks Chen Bing for video-making. In the process of data collection, Hao Lei, Zhou Yafei, Meng Jie, Tian Xue, Yin Shouhang, Liu Ying, Zhai Jing, Wang Kangcheng, Hou Xin, Wei Jiali, Tang Qingting, Hu Jia, Zhang Xing, Ma Yuanxiao, Yang Zhengyu, Mao Yu, Sun Jiangzhou, Hu Na, Liu Xinyi, Yang Bingbing, Zhuang Kaixiang, Shi Liang, Ren Zhiting, Tang Yancheng, Li Hanxiao, Yang Chong, Tang Yan, Lu Dandan, Zhu Wenrong, Guan Jing, Gao Qing, Chen Qunlin, Zhao Yuanfang, Wang Yang, Cao Guoguang, Li Baolin, Dong Debo, Feng Pan, Guo Yiqun, Che Xianwei, Zhao Haichao, Chen Shengdong, Wu Xinran, Deng Xiang, Yang Runlan and others contributed for the project. Thank Kuang Chen for data digitalization. Thanks Ms. Wen Qiong for rear service for the project. The two senior international collaborators, Dr. Michael P. Milham and Dr. Olaf Sporns have been incredible members of the NSFC and CAS team for supporting this longitudinal brain-behavior project in China.

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Table 1 Psychological behavioral scales

Scales	Scope of application (years)	Measuring method	No. of acquisitions	No. of items	Dimensions	Reliability	Validity
Child Behavior Checklist [44,45]	4～16	Guardians' rating	3	120	2	TRR: 0.77～0.79	Factor analysis yielded 2 factors that explain the variance of: 63.0%(males of 4~11 years); 60.2%(females of 4~11 years); 73.4%(males of 12~16 years); 67.4%(females of 12~16 years).
Perceived Stress Scale [46,47]	>10	Self-evaluation	3	14	——	ICR: 0.78	Factor analysis yielded 2 factors; the loadings of the items were between 0.50～0.78.
Adolescent Self-Rating Life Events Checklists [48]	13～20	Self-evaluation	3	27	6	TRR：0.69； ICR：0.85; SHR: 0.88	Factor analysis yielded 6 factors that explained the variance of 44%.
Piers-Harris Children's Self-Concept Scale [49]	6～17	Self-evaluation	1	80	6	TRR: 0.70～0.94; ICR: 0.86; SHR: 0.82	The diagnostic sensitivity of abnormal children was 70%, the specificity was 72%, and the consistency was 0.63 when using the ICD-10 as criteria and the 30th percentile of PHCSS score as demarcation point.
Social Anxiety Scale for Children (SASC) [50]	7～16	Self-evaluation	3	10	2	TRR: 0.54～0.84; ICR: 0.79; SHR: 0.81	Factor analysis yielded 2 factors that explained the variance of 49.21%.
Multidimensional Anxiety Scale [51]	8～19	Self-evaluation	3	39	4	TRR: 0.84；ICR: 0.91	Factor analysis yielded 4 factors; the fit indices of the items were all above 0.94.
State-Trait Anxiety Inventory [52-54]	——	Self-evaluation	3	40	2	TRR: 0.68	Factor analysis yielded 4 factors that explained the variance of 47.1%.
Children's Depression Inventory [55]	7～17	Self-evaluation	3	27	5	TRR: 0.81；ICR: 0.88	Factor analysis yielded 5 factors; the fit indices of the items were all above 0.87.
Children's Loneliness Scale [56]	6～12	Self-evaluation	3	24	——	ICR: 0.88	Confirmatory factor analysis found that the fit indices of the items were all above 0.80.
Positive and Negative Affect Scale [57,58]	——	Self-evaluation	3	18	2	ICR: > 0.77	Factor analysis yielded 4 factors; the loadings of the items were between 0.45～0.80, he fit indices of the items were all above 0.90.
Bar-On Emotional Quotient Inventory [59]	7～18	Self-evaluation	3	60	7	TRR: 0.83; ICR: 0.90	Factor analysis yielded 4 factors that explained the variance of 41.14%.
Eysenck Personality Questionnaire (EPQ) [60]	7～15	Self-evaluation	3	88	4	TRR: 0.58 ～ 0.67 (primary school); TRR: 0.61 ～ 0.86 (middle school)	——
Eysenck Personality Questionnaire (EPQ) [61]	≥ 16	Self-evaluation	3	88	4	SHR of subscales: 0.51～0.77; ICR ：0.54～0.78	——
Torrance Tests of Creative Thinking [62-65]	——	Self-evaluation	1	10	3	——	——
Williams' Creativity Test [66]	——	Self-evaluation	3	50	4	TRR: 0.49～0.81; ICR: 0.40～0.87; SHR: 0.41～0.92	——
Chinese Character Naming [67]	5～12	Experimenters'-rating	3	150	——	SHR: 0.89	——
Video game survey	——	Self-evaluation	1	13	——		——

TRR: Test-retest reliability; ICR: Internal consistency reliability; SHR: Split-half reliability

Table 2 Psychological experimental tasks

Tasks	Testing methods	No. of acquisitions	Introduction of these tasks
Attention Network Test (ANT) [68]	Computer test	3	Subjects were asked to judge the direction of the target correctly and quickly: the arrow in the middle was left or right and pressed the corresponding key.
Task-Switch (TS) [69]	Computer test	3	Subjects were asked to convert between two different types of digital classification tasks (1 to determine the number is greater or less than 5; 2 to determine the number is odd and even numbers)
Working Memory Updating (WM) [70]	Computer test	3	N-back paradigm was used with a total of 9 stimuli for the number of 1~9 were shown successively. Subjects were required to judge whether the current stimulus was consistent with the Nth stimuli presented before.

Table 3 Age distribution of sample size

age span (years)	6~7	7~8	8~9	9~10	10~11	11~12	12~13	13~14	14~15	15~16	16~17	17~18	≥18	total
wave1	7	20	19	19	22	25	11	19	10	11	19	10	0	192
wave2	0	2	16	20	24	18	26	7	14	8	7	11	5	158
wave3	0	0	0	8	27	19	7	18	7	7	6	2	6	107

Table 4 Completion of phenotypic assessments [a)]

wave	MRI	physiology	WISC-IV	psychological behavior questionnaire					psychological experiment tasks		
				feeling	handedness	SASC	EPQ	character naming	ANT	TS	WM
1	191*	192	172	183	189	189	190	192	183	78	79
2	157**	158	131	157	157	158	158	158	155	57	57
3	101***	107	100	101	105	101	105	107	107	53	53

a) *: 191 (1 uncomfortable); **: 157(1 perencephaly); ***: 101 (6 perencephaly)